STATEMENT OF RESEARCH

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Although, there is a long history of the applications of mathematics to biology, only recently has mathematical biology become an accepted branch of applied mathematics. Mathematical biology is now a fast growing, well recognized subject, that involves exciting modern applications of mathematics. The increasing use of mathematics in biology is inevitable as biology becomes more quantitative. The complexity of the biological sciences makes interdisciplinary involvement essential. Both traditional topics, such as population and disease modeling, and new ones, such as those in genomics arising from the accumulation of DNA sequence data, have made mathematical biology an exciting field. My work concentrates on the use of epidemiological approaches to model the spread of emerging and re-emerging infectious diseases and system analysis in the presence of uncertainty.

Since the early 1980s there has been a tremendous effort focused on the mathematical modeling of the human immunodeficiency virus (HIV), the virus which causes AIDS (Acquired Immune Deficiency Syndrome). Genetics studies have found the presence of mutant alleles such as $\Delta 32$ and m303 of CCR5 suggesting resistance or protection against HIV for some individuals [1, 2, 3]. A number of mathematical models have been proposed for understanding HIV transmission and AIDS epidemic [4, 5, 6, 7, 8]. Surprisingly, only a few mathematical models have incorporated genetic heterogeneity when modeling HIV; consequently, they may overestimate the destruction caused by the HIV epidemic and the level of response necessary to control it.

One successful example of a mathematical model with genetic heterogeneity is the approach suggested by me and my co-authors [9], where we investigated the role of three prevention programs (education, vaccination and treatment) in HIV transmission . We classified the HIV infected population into rapid, normal, and slow progressors based on their genetic composition. We computed the basic reproduction number (number of secondary cases produced by a typical infected individual in a entirely susceptible population) and determined the relative contributions of each feature to reducing the spread of HIV. Our results showed that treatment programs or features such as partial genetic resistance, which protect an individual may also complicate disease control in the population as a whole by prolonging the infective period. In order for treatment programs or partial genetic resistance to benefit the population as a whole, they must reduce infectivity more than they prolong it. Our numerical analysis showed a high potential for a public education campaign to reduce the spread

of HIV more than vaccination and treatment campaigns. The reason why an education program is a good option is because reliable vaccination and treatment programs are not yet readily available. In addition, a population-level effort is less costly than an individual level effort such as vaccines and treatment. With sufficient thought and creativity, a sustained, dynamic education campaign should not suffer the same kind of diminishing returns as the vaccination and treatment programs presently in use.

For the last two of years my dissertation research project has been to explore the effects of behavioral changes after a smallpox attack [10]. Events of recent years have heightened our awareness of the potential threat of bioterrorism. Speculative discussions on the possible impact of the deliberate release of viruses such as smallpox into unsuspecting human populations have taken place from time to time over the recent years. Mathematical models of viral transmission and control are important tools for assessing the threat posed by the deliberate release of the smallpox virus and the best means of containing an outbreak. Several recent mathematical models for smallpox outbreaks have been proposed and the effects of various public health interventions such as mass vaccination, isolation of infectives, contact tracing with quarantine and vaccination of contacts, and ring vaccination around infectives have been studied [11, 12, 13, 14, 15]. In addition to the public health interventions, there would be changes in behavior in the affected population in response to a smallpox attack. Many changes in behavior such as closure of public places were observed in cities affected by the 2003 SARS outbreak; these played a key role in the containment of the disease [16]. Surprisingly, none of the mathematical models cited above have incorporated behavioral changes; resulting in an over estimation of the size of the outbreak and the magnitude of the interventions needed to control the smallpox epidemic after an attack. Using a computer simulations model based on a system of differential equations in [10] we verified that behavioral changes are likely to play a key role in minimizing the number of smallpox cases and shortening the epidemic.

The model assumed that some people change their behavior in response to the real or perceived smallpox prevalence in their community. This behavior change is modeled by moving people from a normally active group to a less active group with fewer daily contacts. The net effects of different control policies on smallpox transmission were characterized by their impact on the effective reproduction number, the total smallpox cases and the final epidemic size. Our simulations show that over a wide range of scenarios behavioral changes are important in decreasing the final epidemic size and containing the epidemic sooner. Furthermore, surveillance and early detection of the first case play a

critical role in determining the level of behavior change needed to halt the epidemic quickly and the final size of the epidemic. It is unclear how fast public health officials would respond to an outbreak and how people would react in the face of an epidemic. While recognizing the uncertainties, we argue that plausible case scenarios and not worst case scenarios are needed to both predict the future course of an outbreak and identify the measures needed for its control.

Most recently, I have started to perform simulations of the mixing patterns between age groups using the EpiSimS (Epidemiological Simulation System) data [17]. EpiSimS is a large agent based simulation tool that simulates disease transmission using social networks in the city of Portland, Oregon. Although mixing patterns are thought to be important determinants of the spread of infectious diseases, there have been very few attempts to directly quantify them. Mixing matrices in the form of Who-Acquired-Infection-From-Whom (WAIFW) are widely used in epidemiology modeling to estimate the effective contact rates that lead to the transfer of infection [18]. Using the EpiSimS data, we have been able to determine contact patterns between age groups and duration of contact, which play key roles in disease transmission. Furthermore, we have generated WAIFW matrices that will allow us to determine which contacts will be more likely to acquire an infection [19]. Our preliminary results show that contacts are formed from a wider range of age groups contradicting the prevailing opinion that contacts tend to be within age groups. We have identified some interesting patterns of contact which may have epidemiological implications.

Finally, I have started modeling epidemic outbreaks with age structure and behavioral changes. Age structure in epidemic models has been considered by many authors because of the recognition that transmission dynamics of certain diseases cannot be correctly described by the traditional epidemic models with no age dependence. Differences in susceptibility and death rates are important factors in disease transmission. For example, more than half of the US population has received the smallpox vaccine, and recent findings have shown that most of these individuals still have partial protection against smallpox [20, 21, 22]. This means that if an outbreak were to occur, some people vaccinated years ago would not be infected or would have mild disease, if infected.

Furthermore, the introduction of behavioral changes in a heterogeneously mixing population causes a drastic change in the mixing structure. For example, if schools close during a smallpox outbreak, the daily contacts of children would be replaced by more contacts with their parents. Therefore, one must keep in mind that if an outbreak were to occur, the daily number of contacts of the population could not only decrease but could be replaced by different people in the population.

Consequently, we have constructed a more realistic age structure model for the transmission dynamics of smallpox in a heterogeneous population subjected to residual immunity and behavioral changes [23]. We assumed that knowledge of an smallpox outbreak leads to changes in behavior, resulting in different and fewer contacts. Our goal is to determine the impact of residual immunity and behavioral changes on the final epidemic size. Another goal is to develop an optimal distribution of the smallpox vaccine according to immune status. Therefore it may not be necessary to vaccinate the entire population to halt a smallpox outbreak; instead one could target those people who are at higher risk of infection.

In summary, I am interested in the role of epidemiological modeling approaches and methods on the study of disease dynamics and determining effective control strategies that can help us halt disease transmission. I have worked on and am currently working on several exciting research projects and I am looking forward to meeting more challenges and opportunities in my future research.

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